A Detailed Comparative Assessment of Two Treatment Procedures (Standard Selective Serotonin Reuptake Inhibitors and Rapid-Acting Therapies/Specifically Ketamine) For Patients Suffering from Treatment-Resistant Depression Along with Evaluating the Effectiveness of These Approaches in Alleviating Symptoms and Improving Patient Outcomes: An Original Research Study

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ABSTRACT

Aim

This study aims to compare two treatment procedures (standard selective serotonin reuptake inhibitors and rapid-acting therapies/specifically ketamine) for patients suffering from treatment-resistant depression along with evaluating the effectiveness of these approaches in alleviating symptoms and improving patient outcomes.

Materials and Methods

This study examined 80 patients suffering from severe sadness, hopelessness, and emotional numbness. Of these, 60 patients (ages 18 to 51) were diagnosed with treatment-resistant depression after failing to achieve satisfactory results with at least two antidepressant trials. Eligible participants had a documented diagnosis of Major Depressive Disorder or bipolar disorder, demonstrating insufficient clinical progress despite adequate treatment for a minimum of 6 to 8 weeks. The final cohort of 60 patients was divided into two groups: Group 1 received standard treatment with selective serotonin reuptake inhibitors (SSRIs), while Group 2 explored rapid-acting therapies, specifically ketamine. The intention was to compare the efficacy of these two approaches in improving depressive symptoms and overall patient outcomes, offering insights into potential treatment advantages for those with treatment-resistant depression.

Statistical Analysis and Results

The study focused on a diverse cohort of 60 patients aged 18 to 51, all diagnosed with treatment-resistant depression. Group 1 received selective serotonin reuptake inhibitors (SSRIs), while Group 2 was treated with innovative rapid-acting therapies, particularly ketamine. A comparative analysis assessed treatment efficacy using metrics related to Quality of Life, evaluated through the Pearson Chi-Square test. Group 1's findings (n=30) showed a total score of 19 across various factors, while Group 2 (also n=30) demonstrated higher scores in most areas. Specifically, Group 2 outperformed Group 1 in response rates, effectiveness, and onset of action, efficacy, and maintenance of effect. Lastly, authors also summarize the overall treatment effects analyzed with one-way ANOVA, highlighting the comparative effectiveness and safety of SSRIs versus ketamine in treating treatment-resistant depression.

Conclusion

This study concluded that Ketamine, including IV and intranasal esketamine, is more effective than SSRIs for quickly relieving symptoms. To sustain its benefits, it requires repeated doses, usually twice weekly for two weeks. It is primarily for patients who haven't responded to at least two previous antidepressant treatments and may cause dissociation.

Keywords: Depression, Serotonin, Ketamine, Treatment-Resistant Depression (TRD), Standard Selective Serotonin Reuptake Inhibitors, Rapid-Acting Therapies

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Introduction

Depression is a widespread and serious mood disorder that deeply influences an individual's emotional well-being and overall functionality. This condition manifests as persistent feelings of sadness, hopelessness, and despair that can overshadow even the brightest days. Individuals suffering from depression often experience a profound loss of interest in activities they once found enjoyable, leading to a withdrawal from social interactions and hobbies that previously brought them joy.[1,2] The symptoms of depression are diverse and can encompass a range of physical and emotional challenges. These may include fatigue, changes in appetite or weight, sleep disturbances, and difficulty concentrating. To be classified as depression, these symptoms typically must persist for at least two weeks, creating significant barriers to daily life. As a result, individuals may find it increasingly difficult to perform tasks at work, nurture relationships, and engage in social activities, further exacerbating their sense of isolation.[3,4] The origins of depression are complex and multifaceted, stemming from a combination of neurochemical imbalances in the brain, genetic factors that predispose individuals to mood disorders, and external environmental stressors. These stressors can include traumatic experiences, significant loss, or the challenges posed by chronic illness, all of which can contribute to the onset or aggravation of depressive symptoms.[5,6] Treatment for depression is often a comprehensive approach that combines psychotherapy and pharmacotherapy to address the various dimensions of the disorder. Psychotherapy might include cognitive-behavioural therapy (CBT), which focuses on identifying and altering negative thought patterns, as well as interpersonal therapy, which aims to improve relationships and social functioning. Other therapeutic modalities may also be employed, tailored to meet the unique needs and circumstances of each individual seeking help.[7,8] Medications typically prescribed to manage depression are antidepressants, which aim to correct chemical imbalances in the brain. Treatment-resistant depression (TRD) presents a significant challenge in mental health care, defined as the persistence of major depressive disorder symptoms despite the trial of at least two different classes of antidepressant medications. Individuals with TRD often experience severe symptoms, including profound sadness, hopelessness, and suicidal thoughts. Because traditional treatments may not be effective, care providers may employ more complex strategies, which can include switching between different antidepressants, adding psychotherapy to the treatment plan, or utilising advanced brain stimulation therapies. These therapies can involve techniques such as Electroconvulsive Therapy (ECT), which involves delivering electrical currents to the brain to induce controlled seizures that can alleviate depressive symptoms, or Transcranial Magnetic Stimulation (TMS), a non-invasive procedure that uses magnetic fields to stimulate nerve cells in the brain.[9,10] Among the commonly prescribed antidepressants are Selective Serotonin Reuptake Inhibitors (SSRIs), which work by increasing serotonin levels in the brain, a neurotransmitter linked to mood regulation. SSRIs are often considered first-line treatments for depression and related mental health conditions due to their comparatively lower side effect profiles when contrasted with older antidepressants.[11] Major SSRIs include Fluoxetine (often recognised by the brand name Prozac), Sertraline (Zoloft), Escitalopram (Lexapro), Citalopram (Celexa), and Paroxetine (Paxil). Recently, there has been a significant advancement in psychiatric care known as rapid-acting therapies, which represent a revolutionary approach particularly beneficial for treatment-resistant depression and situations involving acute suicide risk. These therapies are designed to provide rapid relief from depressive symptoms, often within hours or days, rather than the weeks typically required for traditional antidepressants to take effect. Ketamine, a dissociative anaesthetic, has emerged as the prototype for this novel class of glutamatergic antidepressants,

highlighting a paradigm shift towards more immediate therapeutic interventions in the treatment of severe depression.[12,13] This study aims to compare two treatment procedures (standard selective serotonin reuptake inhibitors and rapid-acting therapies/specifically ketamine) for patients suffering from treatment-resistant depression, along with evaluating the effectiveness of these approaches in alleviating symptoms and improving patient outcomes.

Materials and Methods

This study was planned, abstracted and conducted in the Department of Psychiatry, Government Medical College, Jalaun. This comprehensive study focused on a diverse group of 80 patients who presented with overwhelming feelings of unrelenting sadness, pervasive hopelessness, and a profound emotional numbness that seemed all-consuming. All patients were selected from the regular OPD footfall of the Department of Psychiatry, Government Medical College, Jalaun, UP. This study was initiated and completed in the time span of 6 months (From 1st January 2025 to 30th June 2025). Each individual sought relief from these distressing symptoms that significantly impacted their daily lives. After conducting thorough clinical evaluations, it was determined that 60 of these patients spanning both genders and ranging in age from 18 to 51 years met the criteria for a diagnosis of depression. These patients had previously undergone various management strategies for their condition, yet they continued to grapple with their symptoms. Notably, they had not achieved satisfactory results despite receiving at least two different antidepressant medication trials during the same depressive episode. The hallmark features observed in these individuals included an unwavering low mood, anhedonia (the inability to experience pleasure), and considerable functional impairment, which persisted even after multiple treatment attempts. Consequently, these individuals were classified as experiencing treatment-resistant depression. For inclusion in this study, patients needed to have a well-documented diagnosis of either Major Depressive Disorder (MDD) or Bipolar Disorder, conforming to the diagnostic criteria outlined in the DSM-5 or ICD-10. Additionally, potential participants were required to exhibit a lack of clinical progress, typically marked by a less than 50% reduction in depressive symptoms despite receiving adequate pharmacological treatment with antidepressants characterized by appropriate dosages and extended treatment durations, often exceeding 6 to 8 weeks. Moreover, all participants needed to be currently enduring a depressive episode. Exclusion criteria for the study were thoughtfully established. They ruled out individuals diagnosed with psychotic disorders, such as schizophrenia, as well as those with primary neurodegenerative disorders (e.g., dementia). Patients actively struggling with substance abuse disorders, severe personality disorders, or untreated medical conditions that could contribute to their depression, such as hypothyroidism, were also excluded from consideration. Special attention was given to specific medical contraindications regarding the study treatments, which included innovative approaches like ketamine therapy and traditional electroconvulsive therapy (ECT). Furthermore, individuals who had inconsistent medication adherence or had not received suitable dosages or durations of treatments were typically excluded to ensure the findings accurately reflected treatment-resistant cases. Prior to participation, informed consent was meticulously obtained from all patients involved in the study. Ultimately, the final study cohort consisted of 60 patients diagnosed with treatment-resistant depression, each aged between 18 and 51. They were systematically divided into two distinct groups based on their treatment modalities. Group 1 comprised 30 patients who were administered the standard treatment regimen of selective serotonin reuptake inhibitors (SSRIs). In contrast, Group 2 included 30 patients who explored innovative rapid-acting therapies, specifically focusing on ketamine administration. A comparative analysis between these two treatment methodologies was carried out, emphasizing metrics related to the Quality of Life and evaluations conducted by qualified clinicians. The primary objective of this rigorous study was to assess and compare the efficacy of traditional selective serotonin reuptake inhibitors with rapid-acting therapies like ketamine in alleviating depressive symptoms and enhancing overall patient outcomes. This investigation aimed to yield valuable insights into which therapeutic approach might be more advantageous for individuals battling the challenges of treatment-resistant depression.

Statistical Analysis

In this study, we employed SPSS software version 28.0 to conduct a comprehensive statistical analysis of our data. This powerful tool allowed us to effectively interpret and examine various statistical relationships and trends. We employed the chi-square test to evaluate the significance of our findings, effectively comparing proportions across groups. This method ensured our results accurately represented the trends and relationships in the data.

Results

The study involved a carefully selected and diverse cohort of 60 patients, each diagnosed with treatment-resistant depression, a complex condition that often defies conventional treatment options. The participants ranged in age from 18 to 51 years, showcasing a broad spectrum of life experiences and challenges. This group included a fairly balanced representation of males and females, with 31 males and 29 females participating. Detailed demographic characteristics, along with the specific age and gender distributions, can be referenced in Table 1. Additionally, Graph 1 vividly illustrates the demographic breakdown of the cohort, providing a visual representation of the gender composition and age range. To thoroughly assess the effectiveness of different therapeutic approaches, the patients were meticulously divided into two distinct groups, each receiving a specialized treatment regimen tailored to their needs. Group 1 comprised 30 patients who underwent a standard treatment program featuring selective serotonin reuptake inhibitors (SSRIs), a commonly prescribed class of antidepressants. Conversely, Group 2 also consisted of 30 patients, but instead of SSRIs, they were administered innovative rapid-acting therapies, particularly focusing on the use of ketamine a treatment known for its fast-acting effects in alleviating depressive symptoms. A comprehensive comparative analysis was undertaken to examine the efficacy of the two treatment methodologies. This analysis emphasized various metrics related to Quality of Life and patient assessments conducted by trained clinicians. Table 2 presents a detailed overview of Group 1 (n=30), highlighting the experiences of those patients who received SSRIs as their primary treatment for treatment-resistant depression. To rigorously interpret the findings, the researchers employed the Pearson Chi-Square test to assess the significance of various factors influencing treatment outcomes. These factors included response rates, overall effectiveness, onset of action, efficacy, maintenance of effect, reductions on the Hamilton Rating Scale for Depression (HRDS), rates of remission, duration of effectiveness, safety and side effects, along with considerations of cost and accessibility, as well as instances of reduced treatment effectiveness. The corresponding values for these factors in Group 1 were: response rates (2), effectiveness (2), onset of action (3), efficacy (2), maintenance of effect (3), HRDS reduction (1), remission rates (2), duration of effect (2), safety and side effects (1), costs and accessibility (1), culminating in a total score of 19. Similarly, Table 3 outlines the findings for Group 2 (n=30), where patients with treatment-resistant depression underwent treatment with the innovative rapid-acting therapy through ketamine administration. The same metrics were analyzed using the Pearson Chi-Square test for comparison. The results for Group 2 yielded the following values: response (3), effectiveness (3), onset of action (4), efficacy (3), maintenance of effect (4), HRDS reduction (2), remission rate (3), duration of effect (3), safety and side effects (2), cost and accessibility (1), and instances of reduced treatment effectiveness (2). Lastly, Table 4 presents an evaluation of the treatment effects across all groups involved, utilizing one-way ANOVA to assess the overall statistical significance of the outcomes across different therapeutic modalities. This thorough analysis aims to deepen the understanding of the effectiveness and safety profiles of SSRIs in comparison to ketamine in the treatment of patients grappling with treatment-resistant depression.

Table 1: Age & gender based statistical description of contributing patients

Age Group (Yrs)	Male	Female	Total	P value
18-24	6	5	11	0.04*
25-31	7	6	13	0.60
32-38	5	7	12	0.01*
39-45	6	6	12	0.80
46-51	7	5	12	0.50
Total	31	29	60	*Significant
*p<0.05 significant				

Graph 1: Patients demographic distribution and associated details

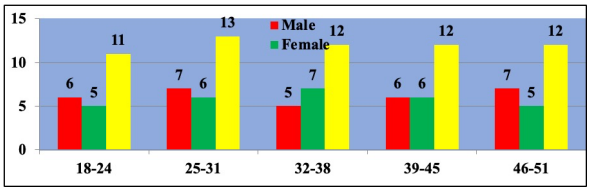

Table 2: Group 1 (n=30) Patients experiencing treatment-resistant depression underwent a regimen involving selective serotonin reuptake inhibitors (SSRIs). To evaluate the significance of the findings from this study, the researchers used the Pearson Chi-Square test

Evaluation	N	Mean	Std. Dev.	Std. Error	95 % CI	Pearson Chi-Square Value	df	p value
Response	2	1.08	1.06	1.05	1.16	1.13	1.12	0.04*
Effectiveness	2	1.08	1.06	1.05	1.16	1.13	1.12	0.04*
Onset of action	3	1.09	1.08	1.07	1.20	1.16	1.14	0.06
Efficacy in TRD	2	1.08	1.06	1.05	1.16	1.13	1.12	0.04*
Maintenance	3	1.09	1.08	1.07	1.20	1.16	1.14	0.06
HRDS reduction	1	1.07	1.05	1.04	1.10	1.09	1.08	0.02*
Remission rate	2	1.08	1.06	1.05	1.16	1.13	1.12	0.04*
Duration of effect	2	1.08	1.06	1.05	1.16	1.13	1.12	0.04*
Safety/side effects	1	1.07	1.05	1.04	1.10	1.09	1.08	0.02*
Cost and accessibility	1	1.07	1.05	1.04	1.10	1.09	1.08	0.02*
Reduced treatment effectiveness	9	2	25	4	22		21	2
*p<0.05 significant								

Table 3: Group 2 (n=30) Patients experiencing treatment-resistant depression underwent a regimen of innovative rapid-acting therapies, specifically focusing on ketamine administration. To evaluate the significance of the findings from this study, the researchers used the Pearson Chi-Square test

Evaluation	N	Mean	Std. Dev.	Std. Error	95 % CI	Pearson Chi-Square Value	df	p value
Response	3	1.09	1.08	1.07	1.20	1.16	1.14	0.06
Effectiveness	3	1.09	1.08	1.07	1.20	1.16	1.14	0.06
Onset of action	4	1.18	1.09	1.10	1.12	1.17	1.18	0.08
Efficacy in TRD	3	1.09	1.08	1.07	1.20	1.16	1.14	0.06
Maintenance	4	1.18	1.09	1.10	1.12	1.17	1.18	0.08
HRDS reduction	2	1.08	1.06	1.05	1.16	1.13	1.12	0.04*
Remission rate	3	1.09	1.08	1.07	1.20	1.16	1.14	0.06
Duration of effect	3	1.09	1.08	1.07	1.20	1.16	1.14	0.06
Safety/side effects	2	1.08	1.06	1.05	1.16	1.13	1.12	0.04*
Cost and accessibility	1	1.07	1.05	1.04	1.10	1.09	1.08	0.02*
Reduced	2	1.08	1.06	1.05	1.16	1.13	1.12	0.04*

treatment effectiveness								
*p<0.05 significant								

Table 4: Estimation amongst all studied groups using one-way ANOVA

Variables	Degree of Freedom	Sum of Squares ∑	Mean Sum of Squares m∑	F	Level of Sig. (p)
Between Groups	9	2.256	2.782	1.4	0.01*
Within Groups	27	2.983	2.820	–	
Cumulative	244.26	80.921	*p<0.05 significant		

Discussion

Liu L et al reviewed in their study that depression is a complex mental health condition characterised by prolonged feelings of sadness, hopelessness, and a general lack of interest in activities that once brought joy. Beyond just mood disturbances, depression can manifest through various physical and psychological symptoms. Individuals may experience significant changes in appetite, leading to noticeable weight loss or gain, alongside sleep disturbances that result in insomnia or hypersomnia.[14,15] Huang C et al. showed in their study that other common symptoms include chronic fatigue, pervasive feelings of worthlessness or guilt, and cognitive impairments that hinder concentration and decision-making. In its most severe forms, depression can lead to suicidal ideation or plans, necessitating immediate intervention. The causes of depression are multifactorial, often stemming from a combination of biological, psychological, and environmental influences. Neurochemical imbalances in the brain, particularly involving neurotransmitters like serotonin, norepinephrine, and dopamine, play a crucial role. Genetic predispositions can also contribute; individuals with a family history of depression may be at an elevated risk. Life events, such as experiencing trauma, significant losses, or enduring chronic illnesses, can further compound the likelihood of developing this disorder. [16,17]Swetlitz et al included in their study that, additionally, risk factors such as major life changes, social isolation, and substance misuse are prevalent within many cases of depression. Depression appears in various forms, with Major Depressive Disorder (MDD) being the most recognised, characterised by severe emotional and physical symptoms that disrupt daily life. Other types include Persistent Depressive Disorder (Dysthymia), Peripartum Depression, Seasonal Affective Disorder (SAD), and Psychotic Depression. Untreated, these conditions can lead to serious health issues and increased suicide risk. Effective treatments are available, such as psychotherapy, particularly Cognitive Behavioural Therapy (CBT), medications like antidepressants, lifestyle changes, and strong social support.[18,19] Cladder-Micus MB et al reviewed in their study that treatment-resistant depression (TRD) presents significant challenges in clinical management and is characterised by individuals who fail to experience significant relief from depressive symptoms despite undergoing at least two different antidepressant treatment trials. Several factors might contribute to the persistence of TRD, including the potential for misdiagnosis and the presence of comorbid conditions such as anxiety disorders or substance abuse, which can complicate the treatment landscape.[20,21] Gaynes BN et al showed in their study that to effectively manage TRD, healthcare providers often need to take a multifaceted approach. This may involve carefully adjusting existing medications, exploring combinations of different pharmacological treatments, or employing more intensive interventions such as Electroconvulsive Therapy (ECT), which has a long history of effectiveness for severe cases. In recent years, rapid-acting treatments like ketamine therapy have garnered attention for their ability to alleviate symptoms in patients experiencing acute distress, showing impressive response rates of 60-70% among individuals diagnosed with TRD.[22,23] Gao R et al. reviewed that this has sparked further investigation into other novel therapies, including esketamine (a nasal spray form of ketamine), GLYX-13 (an experimental drug), and psychedelic compounds such as psilocybin, which have shown potential in clinical trials. As research evolves, it becomes increasingly clear that a comprehensive and personalised approach to treatment is crucial. This not only involves tailoring therapies to individual patient needs but also staying informed about new and emerging treatment options that may offer hope to

those struggling with the profound impacts of treatment-resistant depression.[24,25]

Conclusion

The authors of the study examined two treatment procedures: standard selective serotonin reuptake inhibitors (SSRIs) and rapid-acting therapies, specifically ketamine, for patients suffering from treatment-resistant depression. They evaluated the effectiveness of these approaches in alleviating symptoms and improving patient outcomes. The results indicated and concluded that rapid-acting ketamine, including intravenous (IV) ketamine and intranasal esketamine, is superior to traditional SSRIs in terms of speed of onset and efficacy in reducing depression. While ketamine works quickly, its long-term efficacy necessitates repeated administration (e.g., twice weekly for two weeks) to maintain its initial antidepressant effects. It is important to note that ketamine can have psychotomimetic effects, such as dissociation, and is often reserved for patients who have not responded to at least two previous antidepressant trials.

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